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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/443,542	11/19/1999	FARZAN RASTINEJAD	PC10228A	7363

23913 7590 09/22/2004

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EXAMINER	
MITCHELL, GREGORY W	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/443,542	RASTINEJAD ET AL.	
	Examiner	Art Unit	
	Gregory W Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendments and remarks filed by Applicant on November 19, 2003. Claims 1-25 have been cancelled. Claims 26-35 are pending and are examined herein.

In view of Applicant's amendments and remarks filed on November 19, 2003, Examiner has withdrawn the rejections under 35 U.S.C. 102 and 112 of the previous office action. The following new rejections are made.

Election/Restrictions

Examiner performed a preliminary search on the elected species. Examiner has expanded the search to include the broader genus of compounds sharing the common quinazoline structure of Group I on pages 6 and 7 of Applicant's specification.

Claim Objections

Claim 26 is objected to because of the following informalities: it is terminated with a closed parenthetical; there is no open parenthetical in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claims(s) contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 26-35 are drawn to a method of treating cancer disease states normally associated with possession of a mutant protein of the p53 family. Applicant has further stipulated that the method be comprised of two steps (a) administering an effective amount of an organic non-peptide compound in order to stabilize a protein of the p53 family and (b) "permitting said stabilized protein to interact with one or more macromolecules that participates in a wild-type activity of said protein."

In Applicant's specification, there is an example of an *in vivo* test on pages 49 and 50. The test only discloses the administration of compound X to the animals prior to sacrificing the animals. Applicant does not specify in the claims or specification what positive steps, if any, are involved in the process of "permitting said stabilized protein to interact with one or more macromolecules that participates in a wild-type activity of said protein." Accordingly, it is both unknown and undisclosed what steps are entailed by the second step of the claimed method.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a method of permitting a stabilized protein to interact with one or more macromolecules that participate in a wild-type activity of said protein

Therefore, one of ordinary skill in the art would not have been able to envision what is entailed by the second step of Applicant's method of treating cancer disease states. One of skill in the art would thus have reasonably concluded Applicant was not in possession of the claimed invention for claims 26-35. For examination purposes, step (b) is interpreted as being a passive step wherein following administration of the compound to a subject, the compound is simply allowed to have its effect on the subject.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer disease states normally associated with possession of a mutant protein of the p53 family with specifically disclosed and tested compounds, such as N-{2-[2-(4-methoxy-phenyl)-vinyl]-quinazolin-4-yl}-N',N'-dimethyl-propane-1,3-diamine hydrochloride, does not reasonably provide enablement for a method of treatment of cancer disease states with any "organic non-peptide compound that binds, in said cells, to one or more domains of one or more conformation of said proteins under physiological conditions."

The recitation, "organic non-peptide compound that binds, in said cells, to one or

more domains of one or more conformation of said proteins under physiological conditions," is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim is drawn to an invention which pertains to a method of treating cancer disease states normally associated with possession of a mutant protein of the p53 family with a non-peptide organic compound capable of stabilizing the functionality of a protein of the p53 family.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a treatment comprising the administration to a subject *any* non-peptide organic compound capable of stabilizing the functionality of a protein of the p53 family. The nature of the invention is complex in that

it potentially encompasses any non-peptide organic compound.

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of non-peptide organic compounds would be useful in a method of the instant invention is limited. Applicant discloses a variety of unsaturated bicyclic, tricyclic and tetracyclic heterocyclic and carbocyclic compounds as useful in the invention herein. The specification does not teach that the scope of the invention is limited to these cyclic compounds, however. Indeed, the specification teaches that it is not known which compounds are capable of being used in the instant invention. For example, on page 15 of the specification, in order to determine which compounds may be useful in the instant invention, Applicant states that "compounds may be first screened for interaction with the DBD, performed simultaneously by using a conformational change in the presence of the compound to also detect the interaction with the DBD." Applicant also states on page 4 of the specification that "the invention provides a quick, reliable and accurate method for objectively *identifying* compounds, including human pharmaceuticals, that promote wild-type activity in a protein of the p53 family" (emphasis added).

It is further noted that the claims attempt to further limit the scope of the claims by the function of the compound as opposed to the structure of the compound. Claim 29 is drawn to a treatment utilizing a compound that binds DNA in a specific region. Claim 30 is drawn to a treatment utilizing a compound that binds a wild-type protein. Claim 31 is drawn to a treatment utilizing a compound that targets proteins whose mutation is encoded by an allelic variant. Claim 32 is drawn to a treatment utilizing a

compound wherein the compound binds a mutant protein wherein the mutation is at a specific position on the DNA. While these claims may actually limit the types of compounds that may be used in the instant invention, one of ordinary skill in the art would not be apprised of how these limitations limited the scope of the structure of the compounds useful therein. Therefore, not only would one of ordinary skill in the art not be apprised of the scope of the generic invention, but would not be apprised of the limitations of the dependant claims even if the if the metes and bounds of the independent claim 26 were well defined.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus ..." at 1406 (empahasis added).

In the instant case, "organic non-peptide compound that binds, in said cells, to

one or more domains of one or more conformation of said proteins under physiological conditions," recited in the instant claims is purely a functional distinction. Hence, these functional recitations read on any compounds that might have recited functions. However, the specification merely provides a limited number of examples of compounds in the specification for the various kinds of functional compounds possible.

Thus, Applicant's functional language at the points of novelty fail to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted." *General Electric Co. v. Wabash Appliance Corp.* 37 USPQ at 468 (US 1938).

(4). ***Working Examples***:

Only one particular type working example of an *in vivo* treatment of a cancer disease using a non-peptide organic compound (N-{2-[2-(4-methoxy-phenyl)-vinyl]-quinazolin-4-yl}-N',N'-dimethyl-propane-1,3-diamine hydrochloride) was described in the specification (Figures 5 & 6; and pp. 49-50).

(5). ***State of the Art***:

Applicant admits on page 4 that the state of the art with regard to the use of non-peptide organic compounds for the promotion of wild-type activity in proteins of the p53 family was hitherto unknown, stating that "the present invetion provides the *first demonstration* that non-peptide organic compounds can interact with a protein of the p53 family and promote its wild-type activity." Accordingly, the state of the art with

regard to the instant invention is underdeveloped.

(6). ***Predictability of the Art***:

The invention is directed to a method of treatment utilizing non-peptide organic compounds in general, wherein the structure of those compounds is limited only by the function of the compounds. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Compounds, as described herein, comprising organic non-peptide compound that binds, in said cells, to one or more domains of one or more conformation of said proteins under physiological conditions are, as Applicant has admitted, unknown. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compounds represented by an "organic non-peptide compound that binds,

in said cells, to one or more domains of one or more conformation of said proteins under physiological conditions," which may encompass countless compounds. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any copound represented by "an organic non-peptide compound that binds, in said cells, to one or more domains of one or more conformation of said proteins under physiological conditions." As a result, one of skill in the art would be forced to perform an exhaustive

search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barker (USPN 5616582) in view of both Yaish et al. (*Science*, 1988, 242, 933) and Lee et al. (USPN 5532220).

Barker teaches the use of quinazoline derivatives of the formula I for the treatment of cancer (Abstract). Barker specifically teaches the treatment EGF-type receptor tyrosine kinase sensitive cancer (Claim 1). See, for example, Table III, Example 34, Compound 9^{i}, wherein (6,7-dimethoxy-quinazolin-4-yl)-phenyl-amine is disclosed.

Barker does not specifically teach the treatment of a disease state normally associated with possession of a mutant protein of the p53 family.

Yaish et al. teaches that the EGF receptor is associated with epidermoid carcinoma (p. 933).

Lee et al. teaches that epidermoid carcinoma is associated with a wild-type p53 mutation (col. 6, lines 44-58).

It would have been obvious to one of ordinary skill in the art to treat epidermoid carcinoma with the compounds of formula I, as taught by Barker, because, as taught by Yaish et al., epidermoid carcinomas are associated with EGF-type receptors. Furthermore, it would have been obvious to treat epidermoid cancer with the 2-methyl homolog of the compounds taught by Barker because closely related homologs are obvious. *In re Hass* 141 F.2d 127, 60 USPQ 544 (CCPA 1944). Accordingly, it would have been obvious to treat a cancer disease state normally associated with possession of a mutant protein of the p53 family with a non-peptide compound that binds to one or more domains of one or more of the patient's proteins of the p53 family because (1) it would have been obvious to treat epidermoid carcinoma with a drug within the scope of the instant invention, as described on pages 6 and 7; (2) as taught by Lee et al., epidermoid carcinoma is known to be a cancer disease state normally associated with the possession of a mutant p53 protein; and (3) one cannot separate a compound from its properties and the effect of treating epidermoid carcinoma with a non-peptide organic compound, as defined above, would necessarily have been the stabilization of the functional conformation of p53. Furthermore, it is pointed out that the region of the protein in which the non-peptide organic compound binds, the type of variant utilized to encode the mutant protein to which the compound binds, the cite of mutation of the

protein to which the compound binds, and whether or not the protein that is bound by the protein is wild-type are all intrinsic properties of the non-peptide organic compound and a compound cannot be separated from its properties.

One of ordinary skill in the art would have been motivated to treat epidermal carcinoma, a cancer disease normally associated with the possession of a mutant protein of the p53 family, with the 2-methyl homolog of a compound taught by Barker because of an expectation of similar success to that taught by Barker because minor homologous variants in chemicals are expected to behave in a similar manner.

Response to Arguments

Applicant's arguments with respect to claims 26-35 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8 AM - 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

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